Intensive Care Med (2016) 42:1621–1624
DOI 10.1007/s00134-016-4416-2

WHAT'S NEW IN INTENSIVE CARE

Is the macrocirculation really dissociated from the microcirculation in septic shock?

Glenn Hernández[1*] and Jean-Louis Teboul[2]

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Introduction

Since the landmark paper by De Backer et al. [1], numerous studies have addressed microcirculatory dysfunction in septic shock, established its pathophysiological relevance, and demonstrated the prognostic impact of persistent abnormalities [2–5]. Sublingual microcirculation, which is easy to access with video-microscopic techniques, is the most frequently explored territory in humans. Although up to now these techniques are only recommended for research purposes, continuous technological refinements will probably make them available at the bedside in the future.

A controversial issue is the potential dissociation between sublingual microcirculation and macrohemodynamics in shock states [6]. This is a fundamental issue with potential implications in the selection of the most appropriate resuscitation target. The purpose of this article is to critically analyze the dynamic relationship between macro- and microcirculation during septic shock.

Is the microcirculation really dissociated of macrohemodynamics?

The relationship between macrohemodynamics and microcirculation is conditioned by the predominant pathogenic mechanism in different phases of septic shock. A hypothetical model is presented in Fig. 1. At the early phase, hypovolemia and vascular tone depression predominate, leading to low cardiac output and hypotension (Fig. 1). An early increase in systemic blood flow and/or arterial blood pressure with fluids and/or vasopressors might improve microcirculatory flow and density at this stage [7–9]. This suggests that, at least early on, macro- and microcirculation are not so dissociated, and thus systemic therapies might strongly influence the status of microvascular flow. At a more advanced phase, microvascular and endothelial inflammation predominate, leading to a heterogeneous microcirculatory dysfunction that may fail to respond to systemic blood flow optimization (Fig. 1) [6, 7]. Ospina-Tascon et al. demonstrated that late fluid administration did not improve sublingual microcirculatory flow in spite of an increase in cardiac output [7]. Furthermore, late fluid administration might even worsen tissue oxygenation by deteriorating oxygen diffusion [6]. It is thus likely that microcirculatory abnormalities at this stage are no longer flow-sensitive and could represent an organ dysfunction rather than a resuscitation target. The timing of the transition to this non-flow sensitive stage is unknown, nor whether it is organ-specific.

When can microcirculatory derangements be considered clinically relevant?

Almost all studies performed in septic shock found some degree of alteration of the sublingual microcirculation, leading to the question of when are these derangements clinically relevant [4]. The prognostic significance was brought almost exclusively by the lowest quartiles of severity of alteration of sublingual microcirculation [3, 4] However, severe microcirculatory derangements most often coexist with other markers of severity such as hyperlactatemia, organ dysfunctions and high vasopressor requirements, even if cardiac output and blood pressure have been corrected [4]. In other words, isolated severe sublingual microcirculatory dysfunction appears to be an uncommon event. Additionally, persistent mild to moderate sublingual microcirculatory alterations were still observed in septic shock survivors after early normalization of perfusion-related variables such as capillary refill time, central venous oxygen saturation

*Correspondence: glennguru@gmail.com
[1] Departamento de Medicina, Facultad de Medicina, Pontificia Universidad Católica de Chile, Marcoleta 367, Santiago, Chile
Full author information is available at the end of the article

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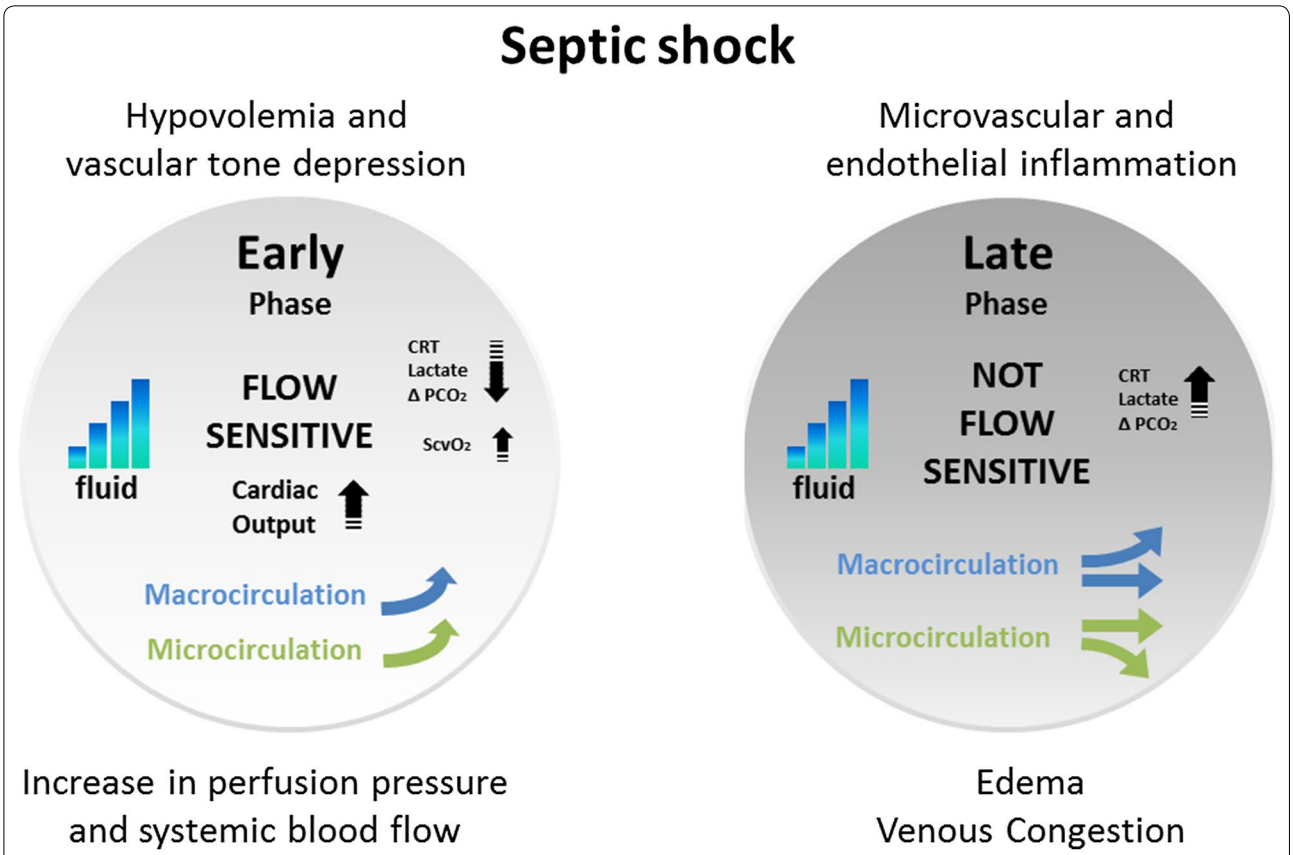

Fig. 1 Under normal physiological conditions, flow is distributed between organs according to demand, and autoregulatory mechanisms at the microcirculatory level maintain tissue perfusion despite changes in systemic blood flow or mean arterial pressure. Hypovolemia and vascular tone depression are the predominant pathogenic mechanisms during the early flow-sensitive phase of septic shock. At this point, increases in perfusion pressure and systemic blood flow lead to an improvement in perfusion-related parameters such as lactate, capillary refill time (*CRT*), central venous–arterial PCO_2 gradient (ΔPCO_2), and central venous O_2 saturation ($ScvO_2$) in parallel to microvascular flow and density. At a later phase, microvascular and endothelial inflammation predominate leading to a heterogeneous microcirculatory dysfunction associated with progressive hypoperfusion that might not respond to systemic blood flow optimization

and venous–arterial PCO_2 gradients [10]. These findings could question the relevance of abnormal sublingual optical images in the absence of clinical hypoperfusion.

Can microcirculatory abnormalities be tracked by systemic perfusion-related parameters?

The presence of systemic hypoperfusion, as demonstrated by hyperlactatemia and/or increased venous–arterial PCO_2 gradients, raises the odds of finding severe sublingual microcirculatory alterations [4, 5]. Profound macrohemodynamic and microcirculatory derangements coexist in unpredictable patterns in patients with progressive septic shock. The cause/effect relationship between these alterations is complex and not completely understood. In progressive septic shock with clear systemic hypoperfusion criteria, as represented by an abnormal skin perfusion or mottling [11], it is safe to assume the presence of severe underlying microcirculatory alterations. However, the treatment strategy is not modified, since the first major clinical responsibility is to rule out whether these abnormalities, either at the systemic or microcirculatory level, are still flow-sensitive. This is particularly relevant since risks of over-resuscitation have been repeatedly demonstrated over the last decade [10]. A multimodal analysis of macrohemodynamics, perfusion variables and eventually of microcirculatory status in the future might help in making the decision of when to stop further resuscitation in septic shock patients [10]. In this regard, a multimodal monitoring including systemic, peripheral, hepatosplanchnic and microcirculatory perfusion parameters was used in a study demonstrating that dobutamine increases systemic flow without affecting tissue perfusion in hyperdynamic septic shock [12].

Practical consequences of the relation between macro-and microcirculation during early septic shock

Several authors have found a favorable impact of systemic blood flow or pressure optimization on microcirculatory variables during early septic shock (Fig. 1) [7–9]. Thus, owing to absence of specific therapies for microcirculatory abnormalities, an option would be to target microcirculatory endpoints to titrate conventional systemic hemodynamic therapies, at least in the early phase of sepsis. Two clinical studies found increased microcirculatory flow after early fluid resuscitation [7, 8]. Another study showed that targeting higher MAP values could improve microcirculatory variables in patients with the worst abnormalities at baseline [13]. However, to make this a real option, microcirculatory assessment should be performed in real time by innovative qualitative approaches, as was recently proposed by the MICRONURSE study [14].

Is the sublingual microcirculation representative of other territories?

Neuro-hormonal activation during shock redistributes flow preferentially to vital organs. Thus, assessment of microcirculatory images in non-vital and non-working organs such as the tongue cannot by definition represent other regions in patients with shock. Accordingly, sublingual microcirculation fails to predict gut mucosal microcirculation in septic patients [15]. This fact might have relevant clinical implications since gut mucosal hypoperfusion is considered an important pathogenic determinant of multiple organ failure in sepsis.

Conclusions

The relationship between macrohemodynamics and microcirculation in septic shock is dynamic and conditioned by the predominant pathogenic mechanism. In an early stage, microcirculatory abnormalities are flow-sensitive and tend to improve with systemic hemodynamic optimization. At this stage, real-time microcirculation assessment could help to select and adjust systemic therapies such as fluids or cardiovascular drugs. In progressive shock, pathophysiological mechanisms are more complex and the relationship between macro- and microcirculation is unpredictable. Further research should be focused on developing technologies to assess microcirculation in more vital organs, and establish criteria to determine when these abnormalities are clinically relevant.

Author details
[1] Departamento de Medicina, Facultad de Medicina, Pontificia Universidad Católica de Chile, Marcoleta 367, Santiago, Chile. [2] Assistance Publique-Hôpitaux de Paris, Hôpitaux universitaires Paris-Sud, Hôpital de Bicêtre, service de réanimation médicale, Le Kremlin-Bicêtre, France.

Compliance with ethical standards

Conflicts of interest
We declare that we have no conflicts of interest.

Received: 19 April 2016 Accepted: 1 June 2016
Published online: 11 June 2016

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